November 14, 2007

Sarah Loftus McLallen
Manager, Diisopropyl Ether HPV Task Group
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. McLallen:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for diisopropyl ether, posted on the ChemRTK HPV Challenge Program Web site on February 17, 2006. I commend the American Chemistry Council Diisopropyl Ether HPV Task Group for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Task Group advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
R. Lee
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Diisopropyl Ether

Summary of SRC Comments

The sponsor, the American Chemistry Council Isopropanol Panel Diisopropyl Ether HPV Task Group, submitted a test plan and robust summaries to EPA for diisopropyl ether (DIPE, CAS No. 108-20-3) dated December 19, 2005. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 17, 2006.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties and Environmental Fate. Adequate data are available for these endpoints for the purposes of the HPV Challenge Program.

2. Health Effects. The submitted data are adequate for the acute, repeated-dose, genetic (gene mutations) and developmental toxicity endpoints. EPA reserves judgment for the genetic (chromosomal aberrations) and reproductive toxicity endpoints pending the submission of more information.

3. Ecological Effects. The submitted data are adequate for acute toxicity to fish. EPA agrees with the submitter's proposal to conduct acute toxicity tests for aquatic invertebrates and algae.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE DIISOPROPYL ETHER CHALLENGE SUBMISSION

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

Adequate data are available for these endpoints for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Adequate data are available for these endpoints for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data are adequate for the acute, repeated-dose, genetic (gene mutations) and developmental toxicity endpoints. EPA reserves judgment for the genetic (chromosomal aberrations) and reproductive toxicity endpoints pending the submission of more information.

Acute Toxicity. The submitted data are minimally adequate. However, the weight of the evidence suggests that there is sufficient information to characterize the acute toxicity of DIPE for the purposes of the HPV Challenge Program.

Repeated-Dose Toxicity. A robust summary needs to be prepared for the 78-week cancer study (Belpoggi et al, 2002) described in the test plan. This could provide important supplemental information from an oral study for the repeat-dose toxicity endpoint (the other studies being via inhalation).

Genetic Toxicity (gene mutations). The test plan states that "DIPE did not induce reverse gene mutation in bacterial tester strains *S. typhimurium* (6 strains), and *E. coli* (3 strains) or mitotic gene conversion in the yeast *S. cerevisiae* JD1, with or without metabolic activation." Gene mutation data were provided in robust summaries for *S. cerevisiae* and five strains of *S. typhimurium*. The submitter needs to provide

robust summaries for the studies using the 6th strain of *S. typhimurium* and the three strains of *E. coli*.

Genetic Toxicity (Chromosomal Aberrations) - owing to several inconsistencies and data gaps in the robust summary provided for a sister chromatid exchange assay, the adequacy of the test could not be determined. There were contradictory descriptions of the type of test performed. The "Type" field of the robust summary indicated "Sister chromatid exchange assay" but the "Method" field indicated "Similar to OECD Guideline 473", which is for a chromosomal aberrations study. For the type of cells tested, the "System of testing" field indicated "Chinese hamster ovary cells" but the lack of metabolic activation employed in this test was justified "because *liver* cells are metabolically competent" (emphasis added). In addition, crucial details about test methodology and results were absent from the summary (see "Specific Comments on Robust Summaries"). The submitter needs to revise this summary to accurately describe the study and results and provide the missing study details.

Reproductive Toxicity. No data were submitted for this endpoint. The test plan indicated that the repeated-dose inhalation study showed evidence of systemic toxicity at 3300 and 7100 ppm but "no changes in reproductive organ weights and structure or sperm and spermatid number" at any tested concentration (maximum 7100 ppm). However, the robust summary in the repeated-dose section of the Data Dossier did not indicate whether the female reproductive organs were examined. The submitter needs to provide a robust summary in the reproductive toxicity section of the Data Dossier that describes the reproductive findings in the repeated-dose study, including data for females if available.

Ecological Effects (fish, invertebrates, and algae)

The submitted data are adequate for acute toxicity to fish. EPA agrees with the submitter's proposal to conduct tests of acute toxicity to invertebrates and toxicity to algae. Because of the volatility of the test substance, closed testing systems using measured concentrations should be used to determine the toxicity of this chemical.

Specific Comments on the Robust Summaries

Health Effects

Genetic Toxicity (Gene mutations). If available, the following missing study details need to be provided for the bacterial reverse mutation assay: specific test concentrations, criteria for positive response, responses of positive and negative controls, number of replicates per test concentration, incubation conditions (temperature, duration), and mean number of revertant colonies per plate.

Genetic Toxicity (Chromosomal aberrations). The submitter needs to resolve the contradictions indicated above. If available, the following missing study details need to be provided for the sister chromatid exchange assay/chromosomal aberrations study: specific test concentrations, number of replicates per test concentration, incubation temperature, and cytotoxicity results. Several details specific to OECD TG 473 were also neglected: number of metaphases scored per concentration, number of cells with aberrations, types of aberrations, and criteria for scoring aberrations. In addition, the test did not include the limit dose for OECD TG 473 and the summary did not indicate whether or not the concentrations tested resulted in cytotoxicity.

Ecological Effects

Fish. Some study details were not included in the robust summary of the critical study for the SIDS endpoint. These details included test substance purity, concentrations tested, lighting period, holding time of fish prior to exposures, mean fish length, biomass loading, number of fish per test concentration, and observed control mortality. In addition, several study details were missing from the two additional studies with *P. promelas*, including test substance purity, control mortality, and holding time of fish prior to exposures.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.